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Treatment Duration for Uncomplicated *Staphylococcus aureus* Bacteremia To Prevent Relapse: Analysis of a Prospective Observational Cohort Study

Yong Pil Chong,[a,c] Song Mi Moon,[a,c] Kyung-Mi Bang,[a,c] Hyun Jung Park,[a,c] So-Youn Park,[a,c] Mi-Na Kim,[b] Ki-Ho Park,[a,c] Sung-Han Kim,[a] Sang-Oh Lee,[a] Sang-Ho Choi,[a] Jin-Yong Jeong,[a,c] Jun Hee Woo,[a] Yang Soo Kim[a,c]

Department of Infectious Diseases[a] and Department of Laboratory Medicine,[b] Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea; Center for Antimicrobial Resistance and Microbial Genetics, University of Ulsan College of Medicine, Seoul, Republic of Korea[c]

Practice guidelines recommend at least 14 days of antibiotic therapy for uncomplicated *Staphylococcus aureus* bacteremia (SAB). However, these recommendations have not been formally evaluated in clinical studies. To evaluate the duration of therapy for uncomplicated SAB, we analyzed data from our prospective cohort of patients with SAB. A prospective observational cohort study was performed in patients with SAB at a tertiary-care hospital in Korea between August 2008 and September 2010. All adult patients with SAB were prospectively enrolled and observed over a 12-week period. Uncomplicated SAB was defined as follows: negative results of follow-up blood cultures at 2 to 4 days, defervescence within 72 h of therapy, no evidence of metastatic infection, and catheter-related bloodstream infection or primary bacteremia without evidence of endocarditis on echocardiography. Of 483 patients with SAB, 111 met the study criteria for uncomplicated SAB. Fifty-three (47.7%) had methicillin-resistant SAB. When short-course therapy (<14 days) and intermediate-course therapy (≥14 days) were compared, the treatment failure rates (10/38 [26.3%] versus 16/73 [21.9%]) and crude mortality (7/38 [18.4%] versus 16/73 [21.9%]) did not differ significantly between the two groups. However, short-course therapy was significantly associated with relapse (3/38 [7.9%] versus 0/73; $P = 0.036$). In multivariate analysis, primary bacteremia was associated with a trend toward increased treatment failure ($P = 0.06$). Therefore, in the treatment of uncomplicated SAB, it seems reasonable to consider at least 14 days of antibiotic therapy to prevent relapse, as practice guidelines recommend. Because of its poor prognosis, primary bacteremia, even with a low risk of complication, should not be treated with short-course therapy.

Traditionally, prolonged courses (4 to 6 weeks) of intravenous antibiotics have been recommended for *Staphylococcus aureus* bacteremia, largely because of concerns that infective endocarditis or other complications, such as deep infection foci or metastatic infections, might be present but undiagnosed (1, 2). However, using this approach for all patients with *S. aureus* bacteremia is expensive and may result in complications of therapy. Several retrospective studies performed in the 1980s to 1990s suggest 10 to 14 days of short-course therapy for *S. aureus* bacteremia with eradicable foci, such as an infected catheter, especially if there is no clinical evidence of early metastatic complications (3–7). However, in these studies, the numbers of patients were small and the proportion of methicillin-resistant *S. aureus* (MRSA) was not usually reported. There is one meta-analysis addressing the efficacy of short-course therapy for catheter-related *S. aureus* bacteremia (8). The meta-analysis found the pooled estimate of the rate of late complications, such as relapse of bacteremia or deep-seated infection, to be 6% in 11 studies. However, those studies had various biases and low statistical precision (8). Therefore, the authors concluded that short-course therapy could not be recommended until randomized trials provided more evidence. Since that meta-analysis, no randomized trial has been performed.

Based on the studies identifying risk factors for complicated *S. aureus* bacteremia (9, 10), the recent Infectious Diseases Society of America (IDSA) guidelines recommend that uncomplicated *S. aureus* bacteremia should be treated with effective antibiotics for at least 14 days (11). The criteria for uncomplicated bacteremia are as follows: (i) exclusion of endocarditis, (ii) no implanted prostheses, (iii) negative results of follow-up blood cultures drawn 2 to 4 days after the initial set, (iv) defervescence within 72 h after the initiation of effective antibiotic therapy, and (v) no evidence of metastatic infection (11). However, these recommendations have not been formally evaluated in clinical studies. The purpose of our study was to evaluate these recommendations regarding the duration of therapy and to provide additional evidence for the management of uncomplicated *S. aureus* bacteremia. Therefore, we analyzed data from our prospective cohort of patients with *S. aureus* bacteremia.

MATERIALS AND METHODS

Study population and design. This prospective observational cohort study was performed in patients with *S. aureus* bacteremia at the Asan Medical Center between August 2008 and September 2010. All adult patients with *S. aureus* bacteremia were prospectively enrolled and observed over a 12-week period. At our hospital, more than 90% of patients with *S. aureus* bacteremia receive infectious-disease consultation, and follow-up blood cultures at 2- to 4-day intervals until negative conversion, echocardiography, adequate infection source control, and parenteral antibiotic therapy for at least 14 days are routinely recommended. Patients were excluded from our study if they had polymicrobial bacteremia, if they died

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Address correspondence to Yang Soo Kim, yskim@amc.seoul.kr.

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or were discharged before positive blood culture results were reported, or if they had clinically insignificant *S. aureus* bacteremia, which means that *S. aureus* was isolated from only one blood culture and the patient did not have clinical findings consistent with bacteremia and had not received antistaphylococcal treatment.

Uncomplicated *S. aureus* bacteremia was defined as (i) negative results of follow-up blood culture at 2 to 4 days after bacteremia, (ii) defervescence within 72 h of therapy, and (iii) no evidence of metastatic infection among patients with catheter-related bloodstream infection (CRBSI) or with primary bacteremia without evidence of endocarditis on transthoracic (TTE) or transesophageal (TEE) echocardiography (11–13). In patients with CRBSI, the infected catheter should have been removed. Patients who died during antibiotic therapy were excluded from the analysis to properly evaluate the clinical outcomes according to the duration of effective parenteral antibiotic therapy. Oral antibiotic therapy was considered to be inappropriate and was not counted in the duration of therapy. We divided patients with uncomplicated *S. aureus* bacteremia into two groups. Group I patients were treated for <14 days (short-course therapy) and group II patients for ≥14 days (intermediate-course therapy) with effective antibiotics. This study was approved by the Asan Medical Center Institutional Review Board.

Data collection and study definitions. Demographic characteristics, laboratory results, underlying diseases or conditions, presence or absence of an intravenous catheter or prosthetic device, severity of the underlying disease, severity of bacteremia, site of infection, antibiogram results, patient management (including infection source control and antimicrobial therapy received), and clinical outcomes were recorded. The severity of bacteremia was assessed using the Pitt bacteremia score (14).

CRBSI was defined according to the Infectious Diseases Society of America guidelines (15, 16); Probable CRBSI was defined as *S. aureus* bacteremia in a patient who has an intravascular device and ≥1 positive blood culture result obtained from the peripheral vein, clinical features of infection, and no apparent source of *S. aureus* bacteremia with the exception of the catheter, whereas CRBSI was defined as "definite" if one of the following was also present: (i) a positive result of semiquantitative (≥15 CFU per catheter segment) catheter culture, whereby *S. aureus* with the same antibiogram was isolated from a catheter segment and blood culture, and (ii) different times to positivity (growth in the blood culture obtained through the catheter was detected at least 2 h earlier than a culture of simultaneously drawn peripheral blood). Primary bacteremia was defined as *S. aureus* bacteremia occurring in the absence of an apparent portal of entry. Infective endocarditis was defined according to modified Duke criteria (17).

Bacteremia was classified as hospital acquired if a positive blood culture was obtained from patients who had been hospitalized for 48 h or longer. Community onset infections were classified as health care associated or community acquired as defined by Friedman et al. (18). Recurrence was defined as the reappearance of *S. aureus* infection after apparently successful completion of antistaphylococcal therapy for uncomplicated *S. aureus* bacteremia. Recurrence was further subclassified as relapse or reinfection (19). Relapse was defined as recurrent *S. aureus* infection with an organism having the same antibiogram and pulsed-field gel electrophoresis (PFGE) pattern. If the pulsed-field gel electrophoresis pattern of a recurrent isolate was different from that of the original infecting strain, the recurrence was considered reinfection.

Patient outcome. Patient outcome measures were relapse of *S. aureus* bacteremia or deep-seated infection, crude mortality, and treatment failure at 12 weeks after *S. aureus* bacteremia. Treatment failure included any of the following: (i) relapse of *S. aureus* bacteremia or deep-seated infection or (ii) death due to any cause after completion of antistaphylococcal therapy and during the 12-week follow-up period.

Microbiological data. All *S. aureus* isolates were identified using standard methods. Antimicrobial susceptibilities were determined using the MicroScan system (Dade Behring, West Sacramento, CA) and the standard criteria of the Clinical and Laboratory Standards Institute. Methicillin resistance was confirmed by PCR detection of the *mecA* gene. Vancomycin MICs of MRSA isolates were determined by the vancomycin Etest (AB Biodisk, Piscataway, NJ) on Mueller-Hinton agar according to the manufacturer's instructions. PFGE was performed as previously described (20). The PFGE patterns of the initial and subsequent strains of *S. aureus* were compared in order to determine whether recurrent *S. aureus* infection represented a relapse.

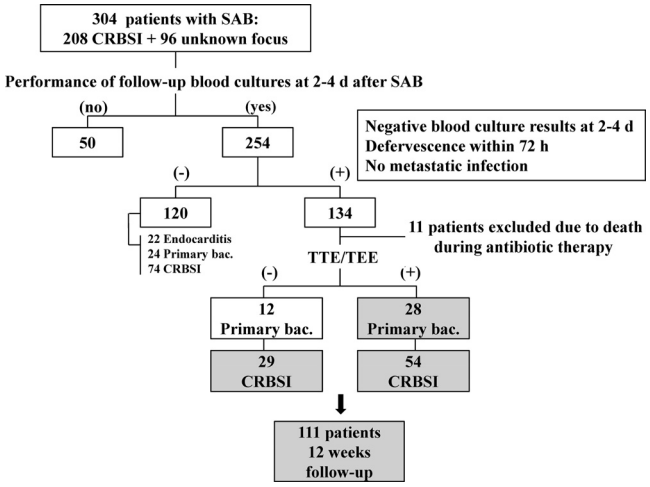

FIG 1 Outline of the patients included in the analysis of uncomplicated *S. aureus* bacteremia (SAB). Primary bac., primary bacteremia; d, days.

Statistical analysis. Categorical variables were compared using the χ^2 test or Fisher's exact test, as appropriate. Continuous variables were compared using nonparametric testing (the Mann-Whitney U test). Univariate analysis of risk factors for treatment failure in all patients was performed. All variables with P values of less than 0.1 in the univariate analysis and other variables of clinical importance were included in the multiple logistic regression model to identify independent risk factors. A two-tailed P value of less than 0.05 was considered statistically significant. All statistical analyses were performed using SPSS software, version 18.0 (SPSS Inc., Chicago, IL).

RESULTS

Study population. During the study period, there were 631 consecutive episodes of *S. aureus* bacteremia at our institution. A total of 148 of these episodes were excluded from the prospective study for the following reasons: polymicrobial bacteremia ($n = 64$), patients not admitted ($n = 69$), and clinically insignificant bacteremia ($n = 15$). All 15 patients with clinically insignificant bacteremia had negative follow-up blood culture results. These patients without clinical signs of infection were not treated with antistaphylococcal antibiotic, as the attending physicians considered a single positive culture a contaminant. Although these patients were not treated, there was no recurrent *S. aureus* bacteremia or deep-seated infection. Four patients died from causes other than *S. aureus* infection at 1 to 2 months after a single positive blood culture result. The remaining 11 patients survived without *S. aureus* infection.

Among a total of 483 patients enrolled in the cohort, 304 (62.9%) had CRBSI or bacteremia with unknown focus (Fig. 1). Follow-up blood cultures obtained at 2 to 4 days after bacteremia, were done in 254 (83.6%) of 304 patients. Of these patients, 134 met the predefined criteria for uncomplicated bacteremia. Eleven patients were excluded, as they had died during antibiotic therapy. TTE (82/82) or TEE (4/82) to rule out infective endocarditis was

TABLE 1 Demographic and clinical characteristics of patients with uncomplicated *S. aureus* bacteremia according to the duration of parenteral antibiotic therapy

Characteristic[a]	No. (%) with characteristic[e]			*P* value
	Total ($n = 111$)	Group I (<14 days)[d] ($n = 38$)	Group II (≥14 days)[d] ($n = 73$)	
Age	60 (49.5–68)	63 (51–73)	59 (49–67)	0.31
Male	67 (60.4)	22 (57.9)	45 (61.6)	0.84
Epidemiologic classification				0.12
Community acquired	2 (1.8)		2 (2.7)	
Health care associated	18 (16.2)	3 (7.9)	15 (20.6)	
Nosocomial	91 (82)	35 (92.1)	56 (76.7)	
MRSA isolate	53 (47.7)	18 (47.4)	35 (47.9)	0.95
Vancomycin MIC (mg/liter)[b]				0.71
≤1	12/45 (26.7)	3/16 (18.8)	9/29 (31)	
1.5	24/45 (53.3)	9/16 (56.2)	15/29 (51.7)	
2	9/45 (20)	4/16 (25)	5/29 (17.3)	
Comorbidity				
Diabetes mellitus	27 (24.3)	9 (23.7)	18 (24.7)	0.91
Hemodialysis dependence	12 (10.8)	2 (5.3)	10 (13.7)	0.21
Immunosuppression	19 (17.1)	7 (18.4)	12 (16.4)	0.79
Liver cirrhosis	29 (26.1)	10 (26.3)	19 (26)	0.97
Malignancy	59 (53.2)	21 (55.3)	38 (52.1)	0.75
Neutropenia	9 (8.1)	1 (2.6)	8 (11)	0.16
Prosthetic device	4 (3.6)	2 (5.3)	2 (2.7)	0.61
No. of comorbidities				0.86
0	17 (15.3)	7 (18.4)	10 (13.7)	
1	48 (43.2)	17 (44.7)	31 (42.5)	
2	30 (27)	8 (21.1)	22 (30.1)	
3	13 (11.7)	5 (13.2)	8 (11)	
4	3 (2.7)	1 (2.6)	2 (2.7)	
Charlson comorbidity index	3 (2–5)	3 (2–5)	3 (2–5.5)	0.49
Pitt bacteremia score	1 (0–2)	1 (0–1)	1 (0–2)	0.22
Type of infection				
Primary bacteremia	28 (25.2)	8 (21.1)	20 (27.4)	0.47
CVC-related infection	52 (46.9)	13 (34.2)	39 (53.4)	0.05
Peripheral catheter-related infection	31 (27.9)	17 (44.7)	14 (19.2)	<0.01
Time to catheter removal[c]	0 (0–2)	0 (0–0.5)	0 (0–2)	0.13
Antibiotic treatment				
MSSA				0.60
Cefazolin	28/58 (48.3)	11/20 (55)	17/38 (44.7)	
Nafcillin	27/58 (46.5)	9/20 (45)	18/38 (47.4)	
Vancomycin	3/58 (5.2)	0/20	3/38 (7.9)	
MRSA				0.35
Linezolid	4/53 (7.5)	2/18 (11.1)	2/35 (5.7)	
Teicoplanin	4/53 (7.5)	0/18	4/35 (11.4)	
Vancomycin	45/53 (85)	16/18 (88.9)	29/35 (82.9)	
Combination therapy	5 (4.5)	1 (2.6)	4 (5.5)	0.66

[a] CVC, central venous catheter.
[b] Percentage of patients who received vancomycin therapy.
[c] All infected catheters were removed.
[d] Duration of parenteral antibiotic therapy (days).
[e] Except for age (years), Charlson comorbidity index, Pitt bacteremia score, and time to catheter removal (days), which are median (IQR).

performed in 82 patients. Twenty-nine patients with uncomplicated CRBSI who did not undergo echocardiography were included in the analysis, as they did not have any clinical features suggestive of endocarditis and were thought to have a low risk of endocarditis, based on the criteria of previous studies (7, 21). Finally, we analyzed 111 patients with uncomplicated *S. aureus* bacteremia. In all of the study patients, infected catheters were removed.

Demographic and clinical characteristics. The demographic and clinical characteristics of 11 patients excluded because of death during antibiotic therapy were as follows: 7 patients had MRSA bacteremia; 10 patients underwent TTE and had no vegetation or valvular abnormality; 3 patients with primary bacteremia who died 6 to 12 days after initiation of treatment had advanced cancer or decompensated liver cirrhosis; and 8 patients who died at 15 to 39 days after initiation of treatment (7 CRBSI and 1 primary bacteremia) had advanced cancer, decompensated liver cirrhosis, or severe pulmonary disease. Of these 11 patients, 10 died from complications of underlying disease during antibiotic treatment for *S. aureus*.

The demographic and clinical characteristics of the 111 patients with uncomplicated *S. aureus* bacteremia are shown in Table 1. The median age was 60 years (interquartile range [IQR], 49.5 to 68 years), and there were 67 (60.4%) male patients. Fifty-three patients (47.7%) had MRSA bacteremia, and only two patients (1.8%) had community-acquired bacteremia. Two treatment groups had similar baseline characteristics and comorbidities that could significantly affect the clinical outcome. However, patients

TABLE 2 Outcomes 12 weeks after *S. aureus* bacteremia in 111 patients according to the duration of parenteral antibiotic therapy

Outcome	No. (%) with outcome			
	Total ($n = 111$)	Group I (<14)[a] ($n = 38$)	Group II (≥ 14)[a] ($n = 73$)	*P* value
Recurrence	4 (3.6)	3 (7.9)	1 (1.4)	0.12
Relapse				
Bacteremia	3 (2.7)	3 (7.9)		0.04
Deep-seated infection				NA[b]
Reinfection				
Bacteremia	1 (1)		1 (1.4)	>0.99
Deep-seated infection				NA
All-cause death	23 (20.7)	7 (18.4)	16 (21.9)	0.67
Treatment failure	27 (24.3)	10 (26.3)	16 (21.9)	0.64

[a] Duration of parenteral antibiotic therapy (days).
[b] NA, not applicable.

in group II ($\geq$14 days of therapy) had a tendency to have community-acquired or health care-associated bacteremia ($P = 0.12$) and were significantly less likely to have peripheral catheter-related infection than patients in group I ($<$14 days of therapy) ($P < 0.01$). Additionally, there was a trend toward early removal of infected catheters among patients in group I ($P = 0.13$).

Antibiotic treatment. All patients received standard doses of antibiotics for *S. aureus* bacteremia. Among 58 patients with methicillin-susceptible *S. aureus* (MSSA) bacteremia, all except 3 received cefazolin (48.3%) or nafcillin (46.6%) (Table 1). The three patients received vancomycin for more than 14 days. All patients with MRSA bacteremia received vancomycin, teicoplanin, or linezolid, and most (84.9%) received vancomycin. Vancomycin trough concentrations were measured in 13 (81.3%) of 16 vancomycin-treated patients in group I and 26 (89.7%) of 29 vancomycin-treated patients in group II. Vancomycin trough concentrations of $\geq$15 μg/ml at steady state were achieved in 11 patients (84.6%) in group I and 17 patients (65.4%) in group II. Five patients received combination therapy, including rifampin (1 patient) or quinolone (4 patients). The types of antibiotics prescribed were similar in the two groups. The median duration of antibiotic therapy was 8.5 days (IQR, 7 to 11 days) in group I and 16 days (IQR, 14 to 21 days) in group II. Oral antibiotics were administered following parenteral antibiotics in five patients (amoxicillin/clavulanate [1 patient], cephradine [3 patients], and moxifloxacin [1 patient]) in group I and in one patient (amoxicillin/clavulanate) in group II. Oral antibiotic therapy was not counted in the duration of therapy.

Treatment outcome. Table 2 shows the 12-week outcomes. After completion of antibiotic treatment, the treatment failure rate in the overall study population was 24.3%, relapse of *S. aureus* bacteremia occurred in three patients (2.7%; 95% confidence interval [CI], 0.6 to 7.7%), and reinfection occurred in one patient. Treatment failure, including relapse of infection and death, occurred less commonly in patients treated for $\geq$14 days; however, this difference was not statistically significant (26.3% in group I versus 21.9% in group II; $P = 0.64$). Patients with primary bacteremia had a tendency to experience more treatment failures than patients with CRBSI (35.7% versus 19.3%; $P = 0.08$). Patients in group I had a tendency to have more recurrence of *S. aureus* bacteremia than patients in group II (7.9% versus 1.4%; $P = 0.12$). Importantly, relapse of *S. aureus* bacteremia occurred only in patients treated for less than 14 days ($P = 0.036$). Relapse in the form of deep-seated infection did not occur. Reinfection occurred in one patient in group II. In this patient, the first bacteremic episode was MSSA CRBSI, and the recurrent bacteremic episode was MRSA CRBSI.

Univariate analysis indicated that risk factors for treatment failure were a high Charlson comorbidity score (odds ratio [OR], 1.46; 95% CI, 1.17 to1.81) and malignancy (OR, 3.93; 95% CI, 1.44 to 10.76). These significant univariate variables, the type of infection, and the duration of antibiotic therapy (group I versus group II) were included in the multivariate logistic regression model. An independent risk factor associated with treatment failure was a high Charlson comorbidity score (adjusted OR, 1.37; 95% CI, 1.06 to 1.76; $P = 0.02$). The duration of antibiotic therapy and malignancy were not significantly associated with treatment failure ($P = 0.45$ and $P = 0.19$, respectively), and primary bacteremia was associated with a trend toward increased treatment failure (adjusted OR, 3.79; 95% CI, 0.93 to 15.43; $P = 0.06$) in multivariate analysis.

Table 3 shows the characteristics of three patients with relapse of *S. aureus* bacteremia. None of these patients had an implanted prosthesis, and all of them underwent echocardiography in order to rule out endocarditis. In these three patients, the duration of antibiotic therapy was 3, 11, and 13 days, respectively, and all relapse episodes were primary bacteremia. Two patients were cured with prolonged antibiotic therapy.

DISCUSSION

In this analysis of a prospective observational cohort study, we evaluated the duration of therapy for uncomplicated *S. aureus* bacteremia as recommended by the IDSA guidelines (11) and found that uncomplicated *S. aureus* bacteremia should be treated for at least 14 days to prevent relapse. In the present study, relapse of bacteremia occurred in 7.9% of the patients who received short-course therapy ($<$14 days). One might thus say that this relapse rate is acceptable in the management of uncomplicated *S. aureus* bacteremia; however, a 7.9% relapse rate is relatively high for the following reasons. It is believed that most relapses occurring as bacteremia or deep-tissue infection after short-course therapy for uncomplicated *S. aureus* bacteremia result from inadequately treated occult endocarditis. Published estimates of the prevalence of endocarditis complicating catheter-related *S. aureus* bacteremia are 2.6 to 38% (8, 22, 23), and the pooled relapse rate of *S. aureus* endocarditis after conventional therapy (4 to 6 weeks) is 2.6% (8). Therefore, the predicted relapse rate after conventional

TABLE 3 Characteristics of three patients with relapse of *S. aureus* bacteremia[a]

Patient	Type of infection	Underlying disease	Time to catheter removal (days)	Duration of treatment (days) (antibiotic)	Relapse episode	Time to relapse (days)	Relapse outcome
1	Primary bacteremia (MSSA)	HCC, no prosthesis		3 (cefazolin)	Primary bacteremia	37	Cure
2	CVC-related infection (MRSA)	ESRD on HD, no prosthesis	4	11 (linezolid)	Primary bacteremia	8	Cure
3	CVC-related infection (MSSA)	LC, no prosthesis	0	13 (nafcillin)	Primary bacteremia	26	Non-SAB-related death

[a] HCC, hepatocellular carcinoma; CVC, central venous catheter; ESRD, end stage renal disease; HD, hemodialysis; LC, liver cirrhosis; SAB, *S. aureus* bacteremia.

therapy for CRBSI can be calculated to be 0.07 to 0.99% (2.6 to 38% × 2.6%). For *S. aureus* bacteremia of unknown origin, the probability of infective endocarditis is low in patients who lack risk factors for complications (10, 21). Therefore, even for the most extreme published estimate of the prevalence of endocarditis in CRBSI and primary bacteremia, the relapse rate after conventional therapy is expected to be less than 1%. In this context, the relapse rate after short-course therapy for uncomplicated *S. aureus* bacteremia should be close to zero. Therefore, the relapse rate of 7.9% in our study is not acceptable, and it seems reasonable that uncomplicated *S. aureus* bacteremia should be treated for at least 14 days.

Community-acquired *S. aureus* bacteremia and absence of a primary source of infection are important risk factors for complicated bacteremia (10, 24). In Nolan and Beaty's study (24), 93% (39/42) of patients without primary staphylococcal lesions had secondary foci (metastatic infections). Therefore, we had designed the present study so that among patients with an unknown focus of *S. aureus* bacteremia, only patients who underwent extensive workups to rule out endocarditis and metastatic infection and had no symptoms or signs of metastatic infection were enrolled. Nonetheless, patients with primary bacteremia in the present study had a tendency to experience more treatment failures ($P = 0.06$). Hence, patients with primary bacteremia should not be treated with short-course therapy, even if they have a low risk of complicated bacteremia. Although there is no direct recommendation for primary bacteremia in the IDSA clinical practice guidelines, a minimum 14 days of therapy is recommended for uncomplicated *S. aureus* bacteremia without evidence of infective endocarditis on echocardiography (11). However, because primary bacteremia and/or community-acquired bacteremia has a high risk of complication (10, 24), and in the present study there was a trend toward higher treatment failure rates in primary bacteremia, primary bacteremia, especially if it is community acquired, should not be considered uncomplicated bacteremia.

There are several observational studies regarding the duration of therapy for *S. aureus* bacteremia, which usually focused on the management of CRBSI or the recurrence of *S. aureus* bacteremia (4–8, 25–30). In these studies, patients had diverse clinical characteristics of *S. aureus* bacteremia with various extents and severities of infection. Some patients had hematogenous spread of infection, persistent bacteremia, or other complications, while others did not have such complications. Consequently, the recommended treatment duration differed among the studies. Determination of the optimal treatment duration, acquired from the analyses of such heterogeneous patient groups, could not be generalized to patients who can be treated by short-course (<14 days) or intermediate-course (at least 14 days) therapy. In the present study, we included only patients with uncomplicated *S. aureus* bacteremia. Therefore, our findings, as acquired from the homogenous patient group, are directly applicable to clinical practice. In general, the adequate treatment duration for infectious diseases needs to be determined by a randomized controlled trial. However, a randomized, controlled, noninferiority trial comparing intermediate-course therapy with conventional therapy (4 to 6 weeks) for uncomplicated *S. aureus* bacteremia could not be easily performed because the relapse rate would be expected to be very low (~1%) and approximately 1,000 patients would be required. Alternatively, an uncontrolled study would seem to be adequate for determining the optimal duration of therapy if the relapse rate is acceptably low. According to this concept, the efficacy of at least 14 days of therapy (for example, 14 to 16 days of therapy) should be verified by another large study.

To determine the duration of therapy in a patient with *S. aureus* bacteremia, endocarditis should be excluded. Although guidelines and many authors recommend TEE rather than TTE to exclude endocarditis (11, 15, 23, 31, 32), TEE is not frequently (18 to 28% of patients) performed in actual clinical practice, and even TTE is performed in only 30 to 61% of patients with *S. aureus* bacteremia (13, 21). The most plausible explanation for the low utilization rate of TEE is that most attending physicians tend to regard it as an invasive procedure and are reluctant to perform it in patients who have uncomplicated bacteremia and show a prompt clinical response to antibiotic treatment. A recent survey reported that even for infectious disease and cardiology specialists, only 41% routinely performed TEE for patients with *S. aureus* bacteremia (33). Also, in the present study, TEE was performed in only four patients with uncomplicated *S. aureus* bacteremia, while most patients (73.9%) underwent TTE. Therefore, there could be a concern that endocarditis was not adequately excluded. However, a recent study documented that TTE can effectively exclude endocarditis in low-risk patients with no metastatic infection (34). In young children with *S. aureus* bacteremia, TTE is considered adequate for ruling out endocarditis, given their thin chest walls (11, 35). Similarly, as Asian patients generally have a lower body mass index (BMI) than Western patients (for example, the prevalence of BMIs of ≥25 kg/m^2 among adults is only 32% in Korea but is 68% in the Unites States) (36), the acoustic window of TTE could be adequate for ruling out endocarditis in our patients with uncomplicated *S. aureus* bacteremia. In the present study, we enrolled 29 patients with uncomplicated CRBSI who had no echocardiographic data, as they were thought to be less likely to have endocarditis based on previous studies (7, 21). Kaasch et al. (21) and Pigrau et al. (7) proposed clinical prediction criteria, such as prolonged bacteremia of >4 days, persistent fever, and metastatic foci, to identify patients with *S. aureus* bacteremia at low risk for endocarditis; the negative predictive value of this criterion set was 99 to 100%, and they suggested that those without any of the criteria may not routinely require TEE. Our patients with uncomplicated CRBSI also did not meet any of these criteria. However, this did not mean that echocardiography may not be required in these patients. Because clinical criteria alone have a low ability to exclude endocarditis (2, 37, 38), all patients with *S. aureus* bacteremia should at least undergo TTE.

In the present study, among 4 patients treated with linezolid, one with CRBSI had a relapse of *S. aureus* bacteremia. One might say that linezolid itself (as a bacteriostatic antibiotic), rather than short-course therapy, would have contributed to relapse of *S. aureus* bacteremia. However, recent data show that the efficacy of linezolid for *S. aureus* infection is superior, or at least comparable, to that of glycopeptides, such as vancomycin or teicoplanin (39–41). Because the oral bioavailability of linezolid is approximately 100%, no dosage adjustment is needed when therapy is changed from the intravenous to the oral route. Therefore, the considerable efficacy and excellent oral bioavailability of linezolid make the drug an attractive therapeutic option by reducing prolonged hospital stays and allowing earlier hospital discharge in patients with uncomplicated *S. aureus* bacteremia.

Our study has several limitations. There were only a small number of study patients, and the study was underpowered, as it

had approximately 55% power to detect an 8% difference in the relapse rate at the 5% significance level when <14 days and ≥14 days of therapy were compared. To increase the study power, a large multicenter study needs to be performed. In addition, although two study groups had similar baseline characteristics and comorbidities, the probabilities of relapse could be different between the two groups due to early catheter removal and more peripheral CRBSI in patients treated for <14 days. However, relapse of bacteremia occurred only in patients treated for <14 days despite a lower probability of relapse. Therefore, less than 14 days of therapy for uncomplicated *S. aureus* bacteremia could be insufficient. Finally, as ultrasonography or contrast-enhanced computed tomography to identify the presence of catheter-associated thrombosis was not routinely performed in patients with CRBSI, infected thrombosis (suppurative thrombophlebitis) would not have been detected in some of our study patients. Crowley et al. reported a 71% incidence of associated venous thromboses in patients with *S. aureus* CRBSI (42). In their study, 44% of patients with venous thrombosis had prolonged bacteremia. If patients with *S. aureus* CRBSI have infected thrombosis, they should be treated for at least 4 weeks (16). There are no data on the incidence of infected thrombosis in patients with CRBSI who satisfy the clinical criteria for uncomplicated *S. aureus* bacteremia. Similar to endocarditis (21), in patients with uncomplicated *S. aureus* bacteremia, the possibility of infected thrombosis associated with CRBSI might be low. However, given the findings of Crowley et al. (42), ultrasonography to exclude venous thrombosis should also be considered in patients with uncomplicated CRBSI before less than 4 weeks of therapy is chosen. Further study of venous thrombosis in uncomplicated CRBSI caused by *S. aureus* is needed.

In conclusion, there were no significant differences in the treatment failure rates and crude mortalities between short-course and intermediate-course therapy for the treatment of uncomplicated *S. aureus* bacteremia. However, less than 14 days of therapy was significantly associated with relapse. A high Charlson comorbidity score was an independent risk factor for treatment failure, and primary bacteremia was associated with a trend toward increased treatment failure. Therefore, it seems reasonable that patients with uncomplicated bacteremia should be treated for at least 14 days with effective antibiotics to prevent relapse, as the IDSA guidelines recommend. Because of increased risk for treatment failure, patients with a high Charlson comorbidity score or primary bacteremia, especially if it is community acquired, should not be treated with short-course therapy. These recommendations need to be further evaluated in a large multicenter study.

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